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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/036,091	10/19/2001	Murali Ramachandra	16930-004610	1998

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EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 11/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/036,091	RAMACHANDRA, MURALI	
	Examiner	Art Unit	
	Ray Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-16,18-23,25-30 and 35* is/are allowed.

6)☒ Claim(s) *17,24,31 and 36-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because:
> It does not identify the city and either state or foreign country of residence of each inventor. The residence information may be provided on either on an application data sheet or supplemental oath or declaration.

Drawings

The drawings are objected to under 37 CFR 1.83(a) because they fail to show the mechanism of regulation of gene expression as described in the specification. Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

The figure illustrates two separate schematics, as such it would be appropriate to label the different parts (e.g., Figure 1A, 1B). First, the figure illustrates a ligand binding an aptamer placed in between a constitutive promoter and a repressor, thereby precluding translation of the repressor. For the sake of clarity the line with arrowheads should be designated as "mRNA" to indicate that the ligand is binding mRNA and not the DNA in the gene construct itself. Without such a designation one could mistakenly interpret the drawing to indicate ligand as binding DNA and precluding *transcription* and not *translation*. The second part of the figure suffers from a

similar deficiency. In addition, appropriate correction should be made in the specification (i.e., Description of the Drawing) to reference any changes made.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:
Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

1. **The claimed invention (claims 26-35) are directed to non-statutory subject matter.**

The claims recite "cells" containing the claimed nucleic acid vectors. The cells can be in a human since the specification contemplates use of the invention to treat cell proliferaqtive disorders in humans, hence the claims read on a part of a human (or the whole person) having the cell within the body. Claims treading on humans are nonstatutory thus claims 26-35 are rejected.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. **Claim 17 and 26-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

Claim 17 seems to be missing the noun "acid". Appropriate correction is required.

Claims 26-35 are unclear and indefinite because they recite "cell" which can be transfected with the nucleic acid of claim 1 either *in vitro* or *in vivo*. Therefore it is unclear if applicant is claiming a cell transformed and then transplanted into an animal (i.e. human) or a cell which

would be *part of* the animal or human or the entire animal or human containing the cell, because the cell is part of the host organism. Redrafting the claims to recite "An isolated cell..."would be remedial.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. **Claims 24, 32-34 and 48-55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.**

The claims are directed to a method of retarding undesirable cell proliferation (i.e. neoplastic cells) comprising administering to the cells a construct comprising a ligand-specific aptamer linked to DNA segment encoding a transcription regulatory protein, where the protein regulates expression of a gene that itself is involved in regulation of cell proliferation. The method exploits the aptamer-ligand binding to preclude expression (translation) of the regulatory protein. With regard to the composition claims (24, 32-34) comprising the recited constructs (and cells) containing a therapeutic gene, the only disclosed use for said compositions is for gene therapy, hence the claims are included in the instant enablement rejection.

The test for enablement is whether one skilled in the art could make use the claimed invention from the disclosure in the specification coupled with information known in the art

1988). Whether undue experimentation is required is not based upon a single factor but instead is a conclusion reached by weighing many factors which are outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). The factors include the following:

Scope/Breadth of the claims. The claims are broad in scope. For example the claims are directed to any transcriptional regulatory polypeptide, including cofactors, be they activators or repressors. In addition, the broadest claims read on any cell proliferation where a regulated gene is the cause of undesirable cell proliferation. Put another way, modulation of a gene through the aptamer-ligand method can be applied to any type of cancer, in any tissue, anywhere in the body. Moreover, the claims are drawn to gene regulation, which implicitly and explicitly involves gene therapy, thus broadening the scope of the claims.

Nature of the invention. The invention is directed to in vivo gene therapy methods of regulating gene expression, all exploiting an aptamer-ligand mechanism. In vivo gene therapy for treatment of a cell proliferative condition is a complex area of biology with multifactorial, multicomplex and multi-mechanistic implications. In addition the claims are directed to compositions that would be used in gene therapy to effectuate gene regulation, which similarly would implicate complex interactions that to date have yet to be elucidated.

Unpredictability of the art. The art is highly unpredictable, because the invention is ultimately directed to gene expression through modulating availability of transcription factors. Transcription factors regulate cell growth, differentiation, response to external/internal stimuli, as well as apoptosis; On its face, the mechanism for such regulation may seem simple, where the transcription regulatory protein binds to specific DNA sequences within the promoter regions of

target genes, thereby modulating expression of these genes. However, this simple model is deceiving in its underlying complexity because of the fact that transcription factors are often members of large protein families that bind to similar DNA sequences, thus raising the possibility that modulating one transcription regulatory protein may in fact result in the unintended consequence of regulating a gene other than the target gene. Especially in the area of gene regulation to retard cancerous cell growth, it would be highly unpredictable without a great deal of non-routine, trial and error experimentation, to elucidate which transcription factors would target genes specifically (*See generally*, Boyd and Farnham, Proc. Soc. Exp. Biol. Med. Oct. 1999; 222(1): 9-28, at p. 9, Abstract).

Furthermore, the claims are directed to in vivo use. However there is nothing in the disclosure that would indicate how one of ordinary skill in the art would overcome certain obstacles that would be presented, were applicant's invention used to regulate gene expression. For example, for the invention to effect target gene expression regulation, the aptamer itself must first be efficiently transcribed, stabilized against rapid degradation, folded properly to bind to its specific ligand and directed to the part of the cell where it can be most effective. Moreover the obstacles can be particular to each aptamer, exacerbating the unpredictability.

Moreover, gene therapy is still a highly unpredictable art within biology and medicine. For example, vectors used to deliver constructs encoding therapeutic products may be erroneously inserted into a particular gene resulting in unknown, adverse or detrimental effects. (*See*, Check, Erika, Feb. 13, 2003, Nature, 421: 678) (citing occurrence of leukemia due to insertion of retroviral vectors used in gene therapy into a particular stretch of DNA); (*see also*,

Juengst, ET. June 2003, BMJ, 326:1410-11)(indicating that gene transfer often has multiple and unpredictable effects on cells).

State of the art. The state of the art is not well developed. Generally the area of gene regulation (i.e. gene therapy) is poorly developed. Perhaps because of the state of the art, there is no guidance in the disclosure as to what protocol one of ordinary skill in the art would follow to effect cancer retardation. The art does provide some guidance in using aptamers as ligands themselves (e.g. for transactivators of genes), but not as molecular translation switches to drive expression of transcriptional regulatory proteins. The closest pertinent art, uses aptamer switches to control expression of a reporter gene in Chinese Hamster Ovary cells, where the constructs are contained and delivered using an expression cassette; the reference does prophetically contemplate that the aptamer switch mechanism can be used in regulation of gene expression. (See, Werstuck and Green, *Controlling Gene Expression in Living Cells Through Small Molecule-RNA Interactions*, Science, Oct. 9, 1998, 282: 296-8) (See whole article, particularly, Abstract, pp. 297-298 and Figs. 2-3).

In addition, as alluded to under unpredictability, the state of art with regard to gene therapy is poorly developed with many questions yet to be answered.

Amount of guidance provided. The specification does not provide any guidance on how one of ordinary skill in the art would use the invention to effect cancer retardation.

Number of working examples. The disclosure does not contain any working examples.

Level of Skill in the art. The level of skill in high, but given that transcription regulation is one of the most complex areas of molecular biology, the level of unpredictability

and lack of working examples, it must be considered that the skilled artisan would have to conduct trial and error experimentation to attempt to practice the claimed invention.

Given the above analysis of the factors that the courts have determined are critical in ascertaining whether the claimed invention is enabled, it is considered that the skilled artisan would have had to have conducted undue and excessive experimentation in order to practice the claimed invention.

4. **Claims 36-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* transcription regulation, does not reasonably provide enablement for *in vivo* transcription regulation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.**

The same analysis viz., enablement discussed above, applies here with regard to *in vivo* embodiments. In sum while it would not be problematic to use the molecular switch in cells in the laboratory, the level of difficulty to practice the invention without undue experimentation would be wholly different for *in vivo* application.

Allowable Subject Matter

Claims 1-16, 18-23, 25-30 and 35 are allowed. The closest prior art teaches aptamer-ligand mediated control of gene expression of a luciferase reporter gene. (See supra, Werstuck and Green).

The prior art is distinguished in that it does not contemplate the aptamer-ligand mediated translation switch in combination with transcription regulatory protein expression as a means of regulating gene targets of said transcription regulatory protein.

Conclusion

Claims 1-16, 18-23, 25-30 and 35 are allowed. Claims 17, 24, 31-34 and 36-55 are rejected. The following prior art made of record and not relied upon is considered pertinent to applicant's disclosure: Werstruck and Green, Science, Oct. 9, 1998, 282: 296-8; Yamamoto et al. Genes to Cells, May 2000, 5: 371-88; and Jayasena, S.D. Clinical Chemistry, Sept. 1999, 45(9): 1628-50. Werstruck and Green teach expression cassettes with promoter, aptamer and polynucleotide encoding luciferase, where the aptamer is specifically bound by Hoechst dye 33258, thereby preventing translation, thus controlling gene expression in CHO cells. (See Abstract, pp. 297-298 and Figs. 2-3). Yamamoto et al. teach ligand specific aptamers used to control gene expression, where the aptamer specifically binds a transactivator protein (i.e. Tat) which binds to specific regulatory elements in the HIV-1 long-terminal repeat promoter. (See Abstract, p. 371 and Fig. 1). Jayasena teaches that aptamers as a class of molecules with ligand specificity can have various uses in diagnostic assays. (See Abstract, pp. 1635-9).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ramin (Ray) Akhavan whose telephone number is 703-305-4454. The examiner can normally be reached on 8:00-4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1123.

DAVID E. [illegible]
PRIMARY EXAMINER